Decision Memo for Collagen Meniscus Implant (CAG-00414N)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) has concluded that the collagen meniscus implant does not improve health outcomes in the Medicare population. Therefore, CMS has determined that the collagen meniscus implant is not reasonable and necessary for the treatment of meniscal injury/tear and we are issuing a national non-coverage determination under §1862(a)(1)(A) of the Social Security Act.

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TO: Administrative File: (CAG-#00414N)
Collagen Meniscus Implant

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SUBJECT: Coverage Decision Memorandum for Collagen Meniscus Implant (CMI)
DATE: May 25, 2010

I. Decision

The Centers for Medicare and Medicaid Services (CMS) has concluded that the collagen meniscus implant does not improve health outcomes in the Medicare population. Therefore, CMS has determined that the collagen meniscus implant is not reasonable and necessary for the treatment of meniscal injury/tear and we are issuing a national non-coverage determination under §1862(a)(1)(A) of the Social Security Act.

II. Background

The knee menisci are wedge-shaped, semi-lunar discs of fibrous tissue located in the knee joint between the ends of the femur and the tibia and fibula. There is a lateral and medial meniscus in each knee. "Meniscal tears are common orthopaedic injuries, affecting patients of various ages and activity levels" (Fabricant and Jokl 2007). The incidence of meniscus injuries has been reported at 61 per 100,000 (Rimington et al. 2009). Medicare Part B claims data for 2007 identified over 125,000 meniscectomies performed on Medicare beneficiaries.

"Meniscus injuries can be divided into 2 groups: traumatic tears and degenerative tears. Traumatic tears occur in a younger population and are usually the result of a discrete traumatic episode. Degenerative tears are thought to progress from intrasubstance degeneration within the menisci" (Rimington et al. 2009). Degenerative tears of the menisci are thought to be part of the normal aging process (Bonamo et al. 1992). "Injuries to a healthy meniscus are induced by compressive force in combination with tibiofemoral rotation in the transverse plane during a movement from flexion to extension or during rapid cutting or pivoting" (Buma et al. 2007). "The pathomechanics of the more complex degenerative tears is still unknown" (Buma et al. 2007).

"Historically, the meniscus was thought to be vestigial tissue; now it is known that the menisci provide mechanical support, localized pressure distribution, and lubrication of the knee joint" (Fabricant and Jokl 2007). Initially, treatment for meniscal tears was total meniscectomy. In 1948, Fairbank concluded, "meniscectomy is not wholly innocuous; it interferes, at least temporarily, with the mechanics of the joint" (Fairbank 1948). In 1968, Jackson summarized that a high proportion of knees after meniscectomy showed degenerative changes. Jackson felt these changes were more frequent than could be accounted for by the normal aging process (Jackson 1968). In 1998, Messner related the substantial change in the therapeutic approach to this common work or sports injury to Fairbank’s discovery of the development of cartilage degeneration and bone remodeling after meniscectomy (Messner and Gao 1998).

"As the biomechanical importance of the meniscus has been revealed, it has become clear that procedures that preserve the meniscus have significant long-term advantages for the patient" (Belzer and Cannon 1993). In 1983, Hamberg noted that the complications from complete meniscectomy led some surgeons to adopt a more conservative approach to treatment of meniscal tears, making partial meniscectomy the preferred technique (Hamberg et al. 1983). Fabricant and Jolk stated, "The definitive treatment of meniscal tear is repair or excision of the pathologic tissue; however, not all patients with meniscal tears require surgical intervention. Asymptomatic meniscal tears are relatively common findings on magnetic resonance imaging (MRI)" (Fabricant and Jokl 2007). Belzer noted that if a meniscus tear could not be repaired, a conservative partial meniscectomy should be undertaken to preserve as much meniscal tissue as possible to decrease the risk of late degenerative changes (Belzer and Cannon 1993).

When meniscal tears are symptomatic, patients usually complain of clicking and pain with activity. At times a tear can displace and cause locking of the knee joint.

Sohn and Moorman describe tear types as usually being classified by the pattern of the tear. They provided a further description of tear types as:

Acute tear patterns, such as vertical, bucket-handle, and radial tears are seen most often in younger patients. Older patients tend to develop degenerative tear patterns, such as horizontal cleavage tears, oblique tears, and complex combinations of patterns. Tears have also been classified as stable or unstable. All partial thickness tears are stable. Full thickness tears differ based on whether the tear is vertical and longitudinal, or radial. Tear types are also commonly classified by their location relative to the peripheral blood supply with labels of red-red, white-white, and red-white. Red-red tears are peripheral and have blood supply to both sides of the tear and thus have the highest chance of healing. White-white tears are central and avascular and thus have the least chance of healing. Red-white tears have vascularity at the peripheral side of the tear and no vascularity on the central side of the tear. These have a mixed ability to heal (Sohn and Moorman 2008).

Treatments of meniscal tears are not without controversy. Menetrey stated, "Meniscectomy in the older patient remains a controversial topic. …Arthroscopic medial meniscectomy in older patients provides 90% good results six years after non-degenerative meniscal tear, but only 20% of good results after degenerative meniscal tear. However, based on this study, neither symptoms nor physical examination are able to differentiate between traumatic meniscal tears and degenerative meniscal changes in older patients" (Menetrey et al. 2002). Belzer felt that meniscus repair should be limited to patients under 50 years of age (Belzer and Cannon 1993). Herrlin stated that there was still no consensus about the treatment of choice for degenerative meniscus tears. Herrlin found arthroscopic partial medial meniscectomy followed by supervised exercise was not superior to supervised exercise alone (Herrlin et al. 2007). Studies have shown limited and conflicting data on whether age, gender, and weight are important factors relative to clinical outcomes after arthroscopic meniscal debridement (Sohn and Moorman 2008). Sohn and Mooreman also felt meniscal debridement should be reserved for unstable, symptomatic tears. In 1996, Rockborn and Gillquist stated, "…knowledge as to the physiological characteristics of knee joint menisci has advanced, but these advances have not been reflected in further adjustment of clinical therapy. On the contrary, we still have little evidence that the previous `advances' in therapy are genuinely superior to the earlier methods with complete removal of the meniscus" (Messner and Gao 1998). Messner also felt that there was no evidence that repair of a tear in the avascular region is better than partial meniscectomy (Messner and Gao 1998). Starke stated that the results found in the literature regarding whether meniscal repair resulted in improved outcomes compared with meniscectomy were equivocal (Stark et al. 2009).

Because of the recognized important functions of the intact menisci and the risk for development of osteoarthrosis after meniscal removal, meniscal replacement has been advocated in cases with extensive meniscal damage or after total meniscectomy (Messner and Gao 1998). Steadman stated, "Replacement of the damaged or lost portion of the meniscus cartilage would seem an appropriate approach to prevent or minimize the progressive degenerative joint disease that may develop as a sequel" (Steadman and Rodkey 2006). The collagen meniscus implant can be used to fill meniscal defects that result from partial meniscectomy. The collagen meniscus implant is not intended to replace the entire meniscus as it requires a meniscal rim for attachment (Rodkey et al. 2008).

The focus of this national coverage analysis (NCA) is on collagen meniscus implants. The collagen meniscus implant is also identified as collagen scaffold (CS) or CMI throughout the literature, FDA documents, and consequently, this document. The literature describes the placement of the collagen meniscus implant through an arthroscopic procedure with an additional incision for capture of the repair needles and tying of the sutures. After debridement of the damaged meniscus, the implant is trimmed to the size of the meniscal defect and sutured into place (Rodkey et al. 1999). No mention is made in the literature of placement of the collagen meniscus implant in combination with a knee arthrotomy procedure.

III. History of Medicare Coverage

Medicare does not currently have a national coverage determination (NCD) on the collagen meniscus implant. When there is no NCD in place, coverage for the procedure is determined at the discretion of the local Medicare contractors.

Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. §1812 (Scope of Part A); §1832 (Scope of Part B); §1861 (Definitions of Services, Institutions, Etc.). The collagen meniscus implant and procedure to implant the collagen meniscus implant may be considered a benefit under Social Security Act as defined under section 1861(s)(1) of the Act when performed by a physician, as defined under section 1861(s)(2)(B) of the Act as a hospital service incident to physicians' services when rendered to hospital outpatients, and as defined under section 1861(b) when rendered to hospital inpatients. This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

August 27, 2009	CMS initiates opening a national coverage analysis for collagen meniscus implant. Initial 30-day public comment period begins.
September 26, 2009	Initial 30-day public comment period closes.
October 20, 2009	Meeting with ReGen Biologics, Inc.
February 24, 2010	Proposed decision memorandum posted to web site.

March 26, 2010	Comment period on proposed decision memorandum ended.

V. Food and Drug Administration (FDA) Status

On December 18, 2008, the FDA provided 510(k) clearance for the ReGen Collagen Scaffold (K082079). As described in the FDA Summary, the ReGen Collagen Scaffold is a resorbable collagen matrix comprised of bovine type I collagen. The indications for use are stated as:

"The ReGen Collagen Scaffold (CS) is intended for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the medial meniscus. In repairing and reinforcing medial meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization."

The ReGen Collagen Scaffold was originally submitted to the FDA under a premarket approval application (PMA). Amid controversy about the 510(K) clearance for the ReGen Collagen Scaffold, the FDA initiated a review of the clearance process for this device. In September 2009, the FDA issued a preliminary report on the Review of the *ReGen Menaflex®: Departure from Processes, Procedures, and Practices Leave the Basis for a Review Decision in Question*. This preliminary report documents findings and recommendations concerning FDA's review and clearance of the ReGen Biologics, Inc., Collagen Scaffold (CS) device for meniscal repair, marketed as Menaflex. It is stated in the report, "These findings indicate that a focused scientific reevaluation of the decision to clear the CS device is warranted, and we conclude with general recommendations for better protecting FDA's internal processes against external pressures."

The ReGen Collagen Scaffold in the only collagen meniscus implant with FDA clearance at this time (currently marketed as Menaflex™ collagen meniscus implant). The FDA has undertaken a reconsideration of the decision to clear ReGen's CS device.

VI. General Methodological Principles

When making national coverage determinations under section 1862(a)(1)(A) of the Social Security Act, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

This summary represents the evidence relating to the treatment of meniscus injuries with the collagen meniscus implant and includes one randomized controlled clinical trial and six small case series. The evidence CMS examines has as its focus health outcomes, i.e., the benefits and harms of a particular treatment. In the treatment of meniscal injuries, the primary focus is a reduction in the pain-related functional activity restriction as opposed to disease and mortality outcomes. Independently assessed, validated instruments are most heavily weighted. The measurement of treatment effect for meniscal injuries is focused on patient based quality of life instruments rather than clinician-based measures. Wright (2009) reported, "It has become apparent from the results of a variety of studies that, in actuality, the validity of these patient-reported outcomes measures is often better than the clinician-based "objective" measures."

A number of knee injury outcomes measures exist, such as the Western Ontario and McMaster Universities Index (WOMAC) (a commonly used disease specific questionnaire to measure treatment effects in patients with osteoarthritis of the knee), the Knee Injury and Osteoarthritis Outcome Score (KOOS) (validated for orthopedic interventions such as anterior cruciate ligament reconstruction, meniscectomy and total knee replacement) (Bekkers et al. 2009), Cincinnati Knee Rating System (validated for ligamentous injuries), International Knee Documentation Committee (IKDC) (validated for patients with various knee disorders) and the Lysholm scale (Wright 2009). A variety of single leg hop tests have been devised and are popular in anterior cruciate ligament outcome studies, with some reported psychometric testing (Hopper et al. 2002).

The IKDC has eighteen questions that measure patient symptoms and function in daily living activities and sports activity (Higgins et al. 2007). Knee treatment outcomes can be graded as A (normal), B (nearly normal), C (abnormal), and D (severely abnormal). The Cincinnati Knee Rating System assesses subjective symptoms and functional activity level and, though it is described as comprehensive, often only a portion of the scale is used. The minimum score is 120 and the maximum score is 420 with the goal of having the highest possible function in each of the categories (there may be a variation in scoring based on the actual subscales used). It has subscales that include symptoms, daily and sports functional activities, physical examination, knee stability testing, radiographic findings, and functional testing (Wright 2009). The Lysholm scale is an eight item questionnaire designed to evaluate patient's function following knee ligament surgery. Knee stability, pain, locking, swelling, stair-climbing, limp, use of a support and squatting are considered on a 100 point scale. It has been validated for use in athletic patients (Marx et al. 2001) and for patients with meniscal injury (Briggs et al. 2006). When instruments are used for treatments, or populations, or in a manner where they have not been validated, their meaning is difficult to interpret.

For direct measurement of the most important symptom - pain, the visual analog scale (VAS) is often used. The VAS typically uses a 0 to 10 point scale with 0 representing no pain and 10 representing the worst possible pain (a 100 point scale is sometimes used). It can be measured over a certain time period (i.e., last three days, last week, etc.) and under various circumstances (i.e., pain at rest, with activities of daily living, or pain with vigorous activity). The Tegner activity scale measures activity level on a scale of 0 to 10 and was developed as an additional instrument to knee specific measures to include the measurement of global activity for the assessment of activity levels in patients with ligament injuries. Each level of the scale represents the ability to perform specific activities. Level 10 corresponds to participation in competitive sports, while level 0 corresponds to the patient on sick leave or receiving a disability pension because of the knee problem. The Tegner activity scale has been validated in patients with meniscal injury (Briggs et al. 2006). While patient satisfaction is extremely important, its measurement is more difficult to interpret (satisfaction has a different meaning to different people); however, it has been shown to follow outcomes that are related to subjective symptoms and function (Wright 2009).

Physiologic measures are also used but their relationship to clinical outcomes is less clear. Histologic examinations have been done on post-surgical tissue looking for tissue-specific regeneration; nonetheless, unless there is clinical correlation this information may not be useful. Radiographs can be examined for evidence of degenerative changes such as osteophytes and other changes as described by Fairbank in 1948 (Fairbank 1948). However, there is considerable discordance between clinical and radiographic knee osteoarthritis (Hannan et al. 2000; Bedson and Croft 2008). The Outerbridge score is an arthroscopic grading of chondral lesions and can suggest advancing degenerative changes, though clinical correlation again is unclear. Agreement between observers for the Outerbridge score has been described as fair (though, generally, not more than one level difference) to moderately accurate. In the arthroscopic diagnosis of cartilage lesions, there is no universal and definitive grading system (Spahn et al. 2008).

B. Discussion of evidence

1. Question:

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all national coverage analyses (NCA): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" For this NCD, the question of interest is:

Is the evidence sufficient to conclude that meniscus repair with collagen meniscus implant will improve health outcomes in the Medicare population with meniscal damage?

2. External technology assessment (TA)

CMS did not commission an external TA for this NCA.

3. Internal technology assessment

CMS performed an extensive literature search utilizing PubMed for controlled trials, cohort or case-control studies, case series studies and systematic reviews evaluating the use of collagen meniscus implants for meniscal repair. The literature search was limited to the English language and specific to the human population, but included studies conducted in all countries, including the United States. Public access information from the FDA website, as well as FDA memoranda and attachments, not available on the FDA website, provided by Senator Charles Grassley of Iowa were also used.

Evidence for the collagen meniscus implant came from the initial FDA premarket approval (PMA) application clinical trial and several small case series reports.

Evidence Summary

Observational Studies

Six small (starting with thirty-four or less patients) case series with clinical outcomes have been published, three of which were sponsored and supported by the manufacturer.

Stone KR, Steadman JR, et al. Regeneration of meniscal cartilage with use of a collagen scaffold. Analysis of preliminary data. JBJS 1997;79:1770-7.

This phase–one, ten patient clinical feasibility trial was conducted at the Stone Clinic in San Francisco for evaluation of the safety and implantability of the collagen implant and its ability to support tissue ingrowth. Patients were included if they had an irreparable tear (undefined by the authors) or major loss (undefined) of meniscal cartilage in a stable or stabilized knee. The average age was 39.3 years, with the oldest patient age 50. One patient withdrew after three months, "because of personal reasons and the pain caused by the operation." Nine patients were reported to have remained in the study for thirty-six months, however, two patients had additional operations: one at twenty-one months (degeneration and pain) and the other at nineteen months (skiing injury). Three measures were used to judge the results (no mention of measure validation).

Table 1. Stone et al. results

Measure	Pre-op	6 mos	12 mos	24 mos	36 mos	Range at 36 mos
activity	3.0	2.4	2.2	2.0	1.9	NR
pain	2.2	NR	NR	NR	0.6	NR
overall knee rating	Not reported (NR)	NR	3.0	2.0	1.4	NR

Note : The outcome measure scales used were described as:
activity -1 point for strenuous activity, 2 points for moderate activity, 3 points for light activity, 4 points for a sedentary lifestyle, and 5 points for an inability to perform sports activity;
pain - 0 points for no pain, 1 point for mild pain, 2 points for moderate pain, 3 points for severe pain;
overall knee rating - 1 point for a normal knee, 2 points for a nearly normal knee, 3 points for an abnormal knee.

The authors stated, "The score for performance, as assessed with the one-leg-hop test, continued to improve with time, increasing from an average of 90 per cent of that of the uninvolved limb at six months to an average of 94 per cent at twelve months." Radiographs at thirty-six months showed no change in the height of the joint space from preoperatively. Serial MRI revealed, "progressive changes over time, indicating ongoing ingrowth and regeneration of tissue." Histologic specimens were examined and, "the regenerated fibrocartilaginous tissue seemed to be similar, in gross and histological appearance, to meniscal cartilage." The authors concluded, "The collagen scaffold appears to be safe for three years, implantable, and able to support tissue ingrowth."

Rodkey WG, Steadman JR, Li ST. A clinical study of collagen meniscus implants to restore the injured meniscus. Clinical Orthopaedics and Related Research 1999;367S:S281-S292.

Rodkey et al. reported on eight patients with a modified implant in a Phase II clinical trial to determine the safety of the implant and its potential efficacy. The study included patients with acute and chronic injuries who had irreparable injury or previous loss of their medial meniscus, ages 18 to 50. All participants were men with the mechanism of original injury in seven of the patients being sports related. Post-operatively patients followed a strict rehabilitation protocol. Follow-up was a range of 24 to 36 months. All patients underwent relook arthroscopy, and some had removal of scar tissue. Patients had biopsies, serial MRI scans, and serologic testing. One was reported to have excessive scar tissue formation and was reported to respond fully to "joint debridement." Results of measures were as follows.

Table 2. Rodkey et al. 1999 results

Patient number	Lysholm scores		Tegner Activity		VAS	
	Pre-op	24 months	Pre-op	24 months	Pre-op	24 months
21001	94	100	9	7	28	0

Patient number	Lysholm scores		Tegner Activity		VAS	
	Pre-op	24 months	Pre-op	24 months	Pre-op	24 months
21002	88	95	5	5	26	3
21003	80	100	7	4	11	0
21005	52	79	7	5	28	4
21009	55	89	9	8	34	0
21020	72	89	10	4	33	0
21011	97	99	6	3	1	4
21012	64	96	6	6	23	3

The authors stated, "The postoperative radiographs revealed no significant progression of Fairbank changes, nor was there any noteworthy change in joint space or in axial alignment based on long standing radiographic films." The serial MRI scans showed, "…there consistently was a decreasing signal intensity with time that suggested an ongoing maturation process of the newly regenerated tissue." Biopsy revealed, "…the collagen meniscus implant was progressively invaded and replaced by cells similar to meniscus fibrochondrocytes with production of new matrix in all patients." The authors concluded, "The collagen meniscus implant seems to be safe for clinical use based on the current study and the previous Phase I study."

Steadman JK, Rodkey WG. Tissue-engineered collagen meniscus implants: 5- to 6- year feasibility study results. Arthroscopy: The Journal of Arthroscopic and Related Surgery 2005;21(5): 515-525.

Steadman and Rodkey reported on the five to six year follow-up of the eight patients (implanted in 1995 and 1996) reported on in Rodkey et al. 1999. They stated that no complications related to the implant were reported. Results are listed in the following table.

Table 3. Steadman and Rodkey 2005 results

Patient number	Lysholm scores		Tegner Activity		VAS	
	Pre-op	5.5-6.3 yrs	Pre-op	5.5-6.3 yrs	Pre-op	5.5-6.3 yrs
21001	94	87	9	7	28	15
21002	88	95	5	6	26	2
21003	80	95	7	7	11	0
21005	52	74	7	4	28	53
21009	55	89	9	8	34	6
21020	72	76	10	6	33	9
21011	97	95	6	4	1	2
21012	64	94	6	6	23	0

Patient number	Lysholm scores		Tegner Activity		VAS	
	Pre-op	5.5-6.3 yrs	Pre-op	5.5-6.3 yrs	Pre-op	5.5-6.3 yrs

The authors stated, "Histologic assessment of tissue biopsy specimens from 3 patients showed the presence of fibrocartilage with a uniform extracellular matrix." However, they later stated that because there was no control, they could not state conclusively that the new tissue was chondroprotective of the adjacent articular cartilage surfaces. The authors concluded, "The presence of a meniscus replacement tissue that remains in place for 5.8 years and does not cause any untoward effects in the knee joint, permits return of physical activity, and has the histologic characteristics of normal meniscus tissue lends strong support to the concept that a collagen meniscus implant can be used to replace irreparable or removed meniscus tissue."

Reguzzoni M, Manelli A, et al. Histology and ultrastructure of a tissue-engineered collagen meniscus before and after implantation. J Biomed Mater Res B Appl Biomater. 2005;74(2):808-816.

Reguzzoni et al. reported on a case series of four patients with irreparable tears of the posterior horn of the medial meniscus that received a collagen meniscus implant. Patients had a mean age of 38 years. The main purpose of the study was to investigate the implant morphology before and after implantation. Biopsy specimens were harvested at six months after implantation. In these four patients at six months, Lysholm scores increased between 27 to 41 points and Tegner activity scores increased two to three levels. At the six month arthroscopic look, the authors stated, "…regeneration of meniscal-like tissue with healing of the implant to the capsule and to the residual meniscal stump was observed in all knees." The authors reported that no complications occurred in the post operative period. They concluded, "The morphological findings of this case series demonstrate that CMI provides a three-dimensional scaffold suitable for colonization by precursor cells and vessels and leading to the formation of a fully functional tissue."

Zaffagnini S, Giodano G, et al. Arthroscopic collagen meniscus implant results at 6 to 8 years follow up. Knee Surg Sports Traumatol Arthorsc 2007;15:175-183.

Zaffagnini et al. was an eight patient case series with follow up between six to eight years (patients implanted between 1997 and 1999) and a mean age of 25 years (range 20-51). Inclusion criteria were an irreparable meniscal tear or previous meniscectomy involving the medial meniscus. While three patients had the implant placed at the time of the medial meniscectomy, five cases had had a previous subtotal meniscectomy done between 1.5 and 10 years prior to the implant being placed. Measures for follow-up were the Cincinnati Knee Rating System, the IKDC, the VAS, the one leg hop test, standing radiographs and MRI.

Table 4. Zaffagnini et al. 2007 results

Patient	Cincinnati Knee Rating system		IKDC		VAS	
	Pre-op	> 5 years	Pre-op	> 5 years	Pre-op	> 5 years
1	280	320	C	B	2	2
2	260	420	C	A	7	3
3	190	420	B	A	6	1
4	210	420	B	A	5	1
5	250	360	C	B	5	2
6	230	410	B	A	6	1
7	240	360	C	B	6	3
8	260	420	C	A	4	1

The authors reported no complications related to the device. The radiographs revealed no changes in six patients (two with pre-existing grade 2 arthritis) and a slight increase in arthritis as judged by a decrease in joint space in two patients. The authors reported, "MRI evaluation showed mixoid degeneration signal at the implant site in five cases, while one patient had no recognizable implant. Two patients had normal signal, with small implant size." The one leg hop test was reported as normal or near normal in all patients. The authors concluded, "In conclusion, the results of a pioneering tissue engineering technique for meniscus regeneration are encouraging."

Bulgheroni P, Murena L, et al. Follow-up of collagen meniscus implant patients: Clinical, radiological, and magnetic resonance imaging results at 5 years. Knee 2009;doi:10.1016/j.knee.2009.08.011.

The objective of the Bulgheroni case series was to evaluate medium term clinical and radiographic results in patients with the collagen meniscus implant for irreparable medial meniscal tears or for persistent pain after meniscectomy. Thirty -four patients received a collagen meniscus implant. The average age was 39 years (range 22 – 58 years). Follow-up ranged from 60 to 76 months. The authors stated that inclusion and exclusion criteria were the same as the Steadman and Zaffagnini studies. Six patients had one prior meniscectomy. Lysholm scores and Tegner activity scores were obtained at preoperative evaluation and at two and five years after surgery. A radiograph was obtained at five years after surgery but no baseline was obtained for comparison. An MRI was performed at two and five years after the implant again with no baseline for comparison. Eight patients had a second arthroscopic look and biopsy at various time points (two patients had hardware removal, two patients had trauma, one patient had a planned look, the other three for pain). The authors reported that six patients were excluded: one patient had continuous swelling, one patient had implant failure at 15 months, and four patients refused an intraarticular injection of contrast fluid. The average Lysholm score improved from an average of 58 preoperatively to 94 at 24 months. The average Tegner activity scores improved from two preoperatively to five at 24 months. It was unclear how many patients were included in the follow-up Lysholm and Tegner activity scores or what the values were for individual patient improvement numbers. Two complications were observed (one patient with paresthesias, one patient with continuous swelling). It was not stated if adverse events were systematically collected. Though radiographs were taken, as there were no comparative studies it was not possible to study degenerative changes. The purpose of the MRI was to study implant morphology and the result was that the implant appeared not to be completely resorbed. The authors stated, "the greatest weakness of this study is lack of a control group" and "Five years after the implant, the regenerated tissue still was not completely similar to a normal meniscus." They concluded, "Our study has shown that the 5-year results of the use of a collagen meniscus implant in patients with irreparable medial meniscus tears with meniscus removal greater than 25% of total meniscus or presence of persistent pain after meniscectomy are encouraging."

Randomized Controlled Trial

Rodkey WG, DeHaven KE, et al. Comparison of the collagen meniscus implant with partial meniscectomy. A prospective randomized trial. JBJS 2008;90:1413-1426.

This article reported on a multicenter clinical trial of collagen meniscus implant with partial meniscectomy versus partial meniscectomy. Sixteen sites participated with twenty-six surgeons. The trial had two study arms that were reportedly controlled and analyzed separately. One arm, called the acute arm, was defined as patients with no prior surgery on the involved meniscus and the second arm, called the chronic arm, was defined as patients that had had three or fewer prior surgical procedures on the involved meniscus.

Patients were all symptomatic with signs and symptoms experienced by patients in the chronic group reported as medial joint line pain, swelling, locking, clicking, and catching. Signs and symptoms in the acute group were not described.

Inclusion criteria as listed in the article were:

- eighteen to sixty years of age
- irreparable injury to or previous partial loss of one medial meniscus, with an intact rim
- knee in neutral alignment with weight-bearing axis falling within the limits of the tibial eminence on standing anteroposterior radiograph.

Exclusion criteria as listed in the article were:

- Outerbridge Grade-IV chondral lesion
- posterior cruciate ligament insufficiency
- concurrent pathological involvement of the lateral meniscus that required repair or excision of > 25% of the lateral meniscus.

Randomization was computer-generated and the sealed envelopes were maintained in a centralized location for all sites. Patients and surgeons were unblinded before the surgery. The authors contended that 494 patients were eligible, however 183 were excluded prior to or at the time of surgery for various reasons that were, "clearly defined prospectively in the original study protocol", "personal reasons," and "protocol violations."

Table 5. Demographics

	Acute Group (n=157)		**Chronic Group (n=154)**	
	collagen meniscus implant	**control**	**collagen meniscus implant**	**control**
Patients enrolled and evaluated	75	82	85	69
Follow-up time (mos)	64	60	60	57
mean	64	60	60	57
range	23-89	16-85	23-90	23-92
Mean Age (yr)	40	40	38	39
male	65	67	61	50
female	10	15	24	19

Patients who received the collagen meniscus implant followed a different post-op protocol, receiving a specific rehabilitation protocol and the requirement of a second-look arthroscopy with biopsy one year after implant placement. Postoperative rehabilitation programs were specific to each treatment group. Control patients had physical therapy which included full weight-bearing and resumption of activity as tolerated. Collagen meniscus implant patients had a locked knee brace immediately postoperatively that was worn for six weeks. The patients progressed to full, unrestricted activity at six months after surgery. Measures collected were Lysholm functional score, Tegner activity scale, and VAS pain scale (0 – 100) during rest, activities of daily living (ADLs), and during high levels of activity. Tegner scores were obtained retrospectively on the basis of patient recall for preinjury level, preoperatively, and postoperatively. The authors defined a measure identified as a Tegner index where they calculated what they called the percentage of lost activity level that was regained as a result of treatment. A Tegner index of 1.0 indicated that the patient regained all of the activity level compared to what they recalled their activity level to be preinjury. Patient satisfaction was measured by the answer to the question, "how satisfied would they be if they had to live with the current condition of their knee." The surgeon at each site solely determined the severity of each complication and whether it was related to the implant. The authors stated, "Reoperation and survival rates were determined through five years of follow-up of all patients." They defined reoperation as an unplanned additional operation as determined by the surgeon's professional judgment. The end point for their survivorship was defined a priori as no unplanned operation on the knee, "as a result of disabling or persistent pain and/or mechanical symptoms that could possibly involve the meniscus."

The authors reported calculation sample sizes a priori which were, "…determined with use of formulae and methods for comparing two independent population means (Lysholm scores and visual analog scale pain scores) and for estimating a population proportion (tissue regrowth)." They expected a 20% drop-out rate, at least 308 patients were needed for a level of statistical significance of p= 0.05 and 80% power. No details were given on the hypothesis of the differences of the treatment versus control outcomes and the a priori definition of trial success. Associations between normally distributed continuous variables were assessed with the Pearson correlation coefficient (it is not stated that a test for normality was done). The authors said that they used the Spearman rho to compare ranks between continuous nonparametric variables. T tests were used to compare continuous variables between groups. Paired t tests were used for continuous variables preoperative and postoperative comparison. Cox regression was employed using outcomes variables at the time of latest follow-up with the covariates of the dichotomous variable of either treatment or control, the duration of follow-up, and whether or not the patient had undergone concurrent reconstruction of the anterior cruciate ligament. Kaplan-Meier was used to analyze time to reoperation to assess the durability of the surgery. The authors stated, "This method provides an estimate of the probability of the proportion of patients with a reoperation at a particular time." Log-rank was used to compare the Kaplan-Meier curves between controls and treatment groups.

The mean VAS, Lysholm scores, and patient self-assessment scores were not different between groups (Table 6).

Table 6. Outcomes data, preoperative compared to last follow-up (range 16 – 92 months)

	Acute Group		**Chronic Group**	
	collagen meniscus implant (N=75)	**control (N=82)**	**collagen meniscus implant (N=82)**	**control (N=69)**
VAS				
Mean change from preop score	16	21	18	18

Mean score at time of last follow-up	5	6	19	21
Lysholm score				
Mean change from preop score	26	28	16	22
Mean score at time of last follow-up	90	87	79	78
Patient self assessment score				
Mean change from preop score	0.9	1.1	0.7	0.9
Mean score at time of last follow-up	1.6	1.6	1.9	2.1

The authors reported, "As demonstrated by the Tegner index, patients in the chronic group who had received a collagen meniscus implant regained significantly more of their lost activity than did the control patients in that group, thus returning closer to their preinjury activity levels. The patients in the chronic group who had received a collagen meniscus implant regained, on the average, 42% of their lost activity level at nearly five years whereas the controls in the chronic group regained only 29% (p= 0.02)." There was no difference between the treatment and control groups in the acute group. The patient satisfaction scores ("how satisfied would they be if they had to live with the current condition of their knee?") for the chronic group revealed that 66% with the collagen meniscus implant and 49% of the control group were very or somewhat satisfied and in the acute group, 82% of the collagen meniscus implant patients and 75% of the control patients were very or somewhat satisfied.

After one year post surgery, 141 treatment patients (88% of 75+ 85) had an arthroscopy to look for these things:

- direct tissue observation,
- measurement of filling defect,
- biopsy for histologic examination and analysis,

- assessment of Outerbridge score.

Contrary to collagen meniscus implant patients, control patients were not required to undergo a planned second-look arthroscopy so none were reported. It was assumed there would be no tissue regrowth and the status of the chondral surfaces was not determined.

Table 7. Meniscus remaining after partial meniscectomy and subsequent defect filing by collagen meniscus implant

	Acute Group		**Chronic Group**	
	collagen meniscus implant	**control**	**collagen meniscus implant**	**control**
Percent meniscus remaining				
Mean and SD%	51+ /-20	59+ /-19	37+ /-20	40+ /-20
N	75	82	85	69
Percent defect filled				
Mean and SD%	45+ /-28	Assumed 0	58+ /-27	Assumed 0
N	65		76	

The Outerbridge score comparison is listed below. The number of patients for whom these measures were taken was unclear.

Table 8. Outerbridge Score

	Acute		**Chronic**	
	collagen meniscus implant	**control**	**collagen meniscus implant**	**control**

At index surgery	1.3	1.2	1.5	1.7
One year follow-up arthroscopy	1.3	Not done	1.3	Not done

The authors reported that the new tissue grossly appeared to be meniscus-like and well integrated with the host meniscus rim. The histological evaluation of collagen meniscus implant biopsy specimens was conducted by an independent pathologist and then a second pathologist performed an independent evaluation of each biopsy specimen. The authors stated, "On the basis of the histological evaluations, the collagen meniscus implant appears to provide a scaffold for the formation of meniscus-like fibrochondrocytic matrix by the host." A rare finding was inflammation of the synovium. The findings of the two independent pathologists were in agreement.

Though radiographs were obtained at one and two years after surgery, the authors did not use the findings due to, "so much variability in the views and techniques used at the sixteen different study sites that the consulting radiologist was unable to make any definitive statements." In addition, radiographs were not obtained on all patients and the authors did not clearly identify how many patients had radiographs.

Complications and adverse events, as defined by the authors as serious or clinically relevant complication that required some form of treatment, are listed below in Table 9. It was not clear what time frame was used. The severity and whether it was related to the implant was determined by the surgeon. The listed complication rate in the collagen meniscus implant patients was 7.5% (12 patients) and 7.3% (11 patients) in the control group. Seven of the twelve in the treatment group were identified as possibly related to the implant. In one instance a skin infection at the portal site that penetrated into the implant (necessitating removal) was judged not related to the collagen implant.

Table 9. "Serious or Clinically Relevant complications in the Study Knee*"

complication	collagen meniscus implant (n)	control (n)
pain	2	7
swelling/effusion/redness	4	1
instability	1	0
infection/fever	1	1
Nerve injury/numbness	1	1
Deep vein thrombosis	1	1
wound-related/other	1	0
Patellofemoral symptoms	1	0
total	12	11

*These complications were classified as serious or clinically relevant by the surgeon-investigator and required some form of treatment.

Reoperation was defined as an additional surgical procedure on the study knee that was outside of the protocol and, as a result of disabling or persistent pain and/or mechanical symptoms, that could possibly involve the meniscus. The authors said this rate was calculated up to five years in the chronic group and the follow-up rate was 96%. They calculated a 9.5% reoperation rate for collagen meniscus implant patients and a 22.7% rate for the control patients (Table 10). With this data, they calculated a Kaplan-Meier survivorship curve (Log-rank was used to compare the Kaplan -Meier curves between controls and treatment groups) where they claimed the survival rate was 89% for collagen meniscus implant patients and 74% for the control patients (p= 0.04) at five years. They also stated, "...the majority of the reoperations in the controls occurred prior to twenty-four months but only four of the reoperations in the patients treated with a collagen meniscus implant occurred prior to twenty-four months." In the acute study group, there was no difference in reoperation rates and survival rates between the two groups.

Table 10. Reoperations

	Acute		**Chronic**	
	collagen meniscus implant (N= 5)	**control (N= 5)**	**collagen meniscus implant (N= 8)**	**Control (N=15)**
Primary presenting symptom				
pain	2	4	5	11
swelling/effusion	1	0	2	1
stiffness/decreased motion	1	0	0	0
locking/catching/popping	0	0	1	2
instability	1	1	0	1
Primary surgical procedure performed				
Explant of collagen meniscus implant	1	0	2	0

Repeat partial meniscectomy	0	3	1	3
Allograft meniscus transplant	0	0	0	1
High tibial osteotomy	0	0	1	1
Joint debridement/synovectomy/loose body removal	3	1	4	9
Ligament stabilization	1	1	0	1

The authors concluded that, "...the collagen meniscus implant supports new tissue ingrowth that appears to be adequate to enhance meniscal function as evidenced by improved clinical outcomes in patients with a chronic meniscal injury. …The implant was not found to have any benefit for patients with an acute injury."

FDA information

The FDA has access to the raw data from the clinical trial and conducts an independent analysis of the complete data. Additional data was obtained from the following FDA documents.

Food and Drug Administration. Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee Meeting November 14, 2008. FDA executive summary for ReGen Collagen Scaffold. (http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4400b1-01FDA%20Summary%20and%20Questions%20.pdf.

Food and Drug Administration 510(K) Memorandum, subject K082079, ReGen Collagen Scaffold (CS), August 14, 2008. Provided as attachment to letter to CMS from Senator Charles E. Grassley, September 30, 2009.

Pre-Clinical Information. (FDA Executive Summary November 14, 2008 meeting).

"Specifically, FDA requested a comparison of the tensile strength and suture pull-out strength of human meniscus compared to the tensile strength and suture pull-out strength of the ReGen CS device to demonstrate that the device has adequate mechanical properties that approximate those of the removed meniscus and can withstand the functional demands placed upon it over a multi-year period of time prior to complete resorption." "The sponsor provided data on the suture pull-out strength for native canine meniscal tissue as a comparison." "Based on the animal testing data provided, the ReGen CS has 3.5 - 6 times lower suture pull-out strength when compared to native canine meniscus suture pull-out strength." These were the only data presented to the FDA on this topic.

Clinical information
Study Overview

The Rodkey 2008 article was based on the FDA IDE study (G920211). The phase I and phase II feasibility studies for this IDE were approved on July 8, 1993 and August 18, 1995, respectively. The multi-center clinical trial for this IDE was approved in August, 1996. Enrollment was completed April 2003 (FDA Executive Summary November 14, 2008 meeting). Comparing the two study arms (acute and chronic), the only protocol difference was the number of prior meniscus surgeries the patients had upon entering the study (FDA Executive Summary November 14, 2008 meeting). Follow-up visits occurred at one to seven days, six weeks, three and six months, and annually thereafter. The objective of the IDE study was to assess the safety and clinical benefit of the device (FDA Executive Summary November 14, 2008 meeting).

"An individual patient's success was to be determined as follows:

Primary Clinical endpoints:	VAS, Lysholm score, patient's self-assessment. A clinically significant improvement in any two of these three endpoints would be considered a success.
Surrogate endpoints:	Implant status as assessed using arthroscopy, histopathology, and radiographs. Improvement in any two of these three endpoints would be considered a success." (FDA Executive Summary November 14, 2008 meeting)

The IDE protocol did not pre-define a criterion for overall success based on a composite primary endpoint and, as the study sample size calculation was based on both VAS pain score and Lysholm score and no multiplicity adjustment was to be made, the study would be considered an overall success only if the study succeeds on both endpoints (FDA 510(K) Memorandum K082079 August 14, 2008, statistical reviewer).

Patient Population (FDA Executive Summary November 14, 2008 meeting).

Patients were to be between 18 and 60 years of age and in good health, except for damage to the medial meniscus. Additional inclusion criteria included no scientific evidence of progression in healing (no spontaneous repair or regeneration of the meniscus). Additional exclusion criteria included: a history of drug or substance abuse, severe trauma other than as defined in the protocol, and clinically significant (as defined by the investigator) renal, hepatic, cardiac, endocrine, hematologic, autoimmune or any systemic disease which may make implementation/interpretation of the protocol or results difficult.

Surgical Technique (FDA Executive Summary November 14, 2008 meeting).

All surgical lesions (control and treatment) were to be full thickness, extend into the vascular zone, and have an intact meniscal rim. In the chronic arm, treatment patients had an average of 63% of meniscus tissue removed during partial meniscectomy with the control group having an average of 60% of meniscus tissue removed. In the treatment group, 43% (37/87) had 20% or less of native tissue remaining, meaning that in this group there was only 10% of the meniscus left anteriorly and 10% left posteriorly. Put another way, in more than 40% of cases in the chronic group, 80% or more of the native meniscus was removed in the treatment group.

Rehabilitation (FDA Executive Summary November 14, 2008 meeting)

"There is a noted difference in the rehabilitation necessary for the ReGen CS implant (up to 6 months) in comparison to the control, i.e., partial meniscectomy (~ 2-3 weeks)."

Study Endpoints (FDA Executive Summary November 14, 2008 meeting)

Prospectively defined endpoints are listed in Appendix B.

Table 11. Patient Accounting (FDA Executive Summary November 14, 2008 meeting) (FDA 510(K) Memorandum K082079 August 14, 2008).
Chronic Study Arm Only

	pre-op	**post-op**	**6wk**	**3mo**	**6mo**	**12mo**	**24mo**	**36mo**	**48mo**	**60mo**	**72mo**	**84mo**
Theoretical (calculated)	87	87	86	85	82	81	80	80	66	52	42	35
actual	87	87	85	84	80	73	68	38	27	25	24	18
LTF*	0	0	0	0	0	0	1	1	2	2	2	2

	pre-op	post-op	6wk	3mo	6mo	12mo	24mo	36mo	48mo	60mo	72mo	84mo
excluded	0	0	0	0	0	0	2	2	2	2	2	2
withdrew	0	0	0	0	0	1	1	1	1	1	1	1
Not yet due	0	0	0	0	0	0	0	0	14	28	38	45
explants	0	0	1	2	5	5	5	5	5	5	5	5
deaths	0	0	0	0	0	1	2	2	2	2	2	2
% follow-up (calculated)	100%	100%	99%	99%	98%	90%	85%	47%	41%	48%	57%	51%

*loss to follow-up

The FDA information noted that it was not clear what the sponsor meant by the term "actual," (i.e., if the sponsor had some data on a patient or all of the data on the patient per the IDE protocol) (FDA 510(K) Memorandum K082079 August 14, 2008). The FDA executive summary noted, "At the 3-7 year follow-up timepoints, there is approximately 50% of the data available. It is not clear how the missing data has impacted the presentation of the safety and effectiveness endpoints at time-points later than 24 months. The primary endpoint was a 24-month endpoint."

Table 12. Safety Data - Chronic Arm only (FDA Executive Summary November 14, 2008 meeting).

	Results in 510(K)	
	collagen meniscus implant	**control**

Safety		
Serum (blood analysis-ELISA-Antibody)	Not statistically significant difference	
Adverse events		
• Serious AE ○ total events/total patients ○ patient with events/total patients	37/87 (43%) 21/87 (24%)	23/69 (33%) 14/69 (20%)
• Serious device related AE ○ total events/total patients ○ patients with events/total patients	14/87 (16%) 8/87 (9.2%)	2/69 (3%)* 1/69 (1.4%)*
• Non serious device related AE ○ total events/total patients ○ patients with events/total patients	51/87 (59%) 29/87 (33%)	5/69 (7%)* 3/69 (4.3%)*
• Non-serious AE ○ total events/total patients ○ patients with events/total patients	241/87 (277%) 71/87 (82%)	201/69 (291%) 49/69 (71%)
• All AE ○ total events/total patients ○ patients with events/total patients	295/87 (339%) 74/87 (85%)	240/69 (348%) 54/69 (78%)

*Some of the Adverse Events were categorized as "device related" for the partial meniscectomy control by the sponsor even though they did not have a device (unclear why this was done).

Table 13. Adverse events, acute and chronic groups (FDA 510(K) Memorandum K082079 August 14, 2008)

	collagen meniscus implant
Definitely device related	7
Probably device related	18
Possibly related	65
Total from both protocols	162
Adverse events/total patients for each group	(7+ 18+ 65)/(87+ 75)*100 = 56% device related AEs

Re-operations

Table 14. Summary of re-operation data (FDA Executive Summary November 14, 2008 meeting) – Number of Additional Procedures following index procedure for Chronic Study Arm.

	collagen meniscus implant		control	
	# Procedures	**# Patients**	**# Procedures**	**# Patients**
Included: • Reoperations related to meniscal pathology or symptoms	15	14	11	11
Included: • Reoperatons-procedure related	3	3	0	0
Excluded: • Reoperations related to protocol procedure and (2nd look); and/or • Reoperations not procedure or device related	9	7*	9	6*
Total Reoperations Included	18	17	11	11
Total Reoperations	27	24	20	17

*Some patients had repeat /multiple operations

The FDA Executive Summary noted that the JBJS article presented the reoperations differently. The following re-operations were not included in the article regarding the chronic study arm:

- 5 re-operations in the partial meniscectomy (control) patients;
- and, 17 re-operations in the CS device patients" (FDA Executive Summary November 14, 2008 meeting).

Further, for the chronic study arm, "The following reasons were given in the 510(K) for removing these re-operations from the final counts. They were either:

1. A re-operation on the same patients (n= 4 in CS group, n= 5 in control group),
2. A procedure performed during the 1-year arthroscopic re-look (n= 10 in CS group), or
3. The sponsor stated that the re-operation was not related to the meniscus (n= 3, evaluation of saphenous nerve, excision of neuroma, and infection/device removal)." (FDA Executive Summary November 14, 2008 meeting)

Explants

Six devices were explanted in five patients in the chronic group: mechanical failure of the device (n= 5), and infection (n= 1). Depending on which patients are included, eight devices were explanted (FDA 510(K) Memorandum K082079 August 14, 2008).

Effectiveness Endpoints (Source for Tables 15 through 22 - FDA 510(K) Memorandum K082079 August 14, 2008).

Clinical endpoints were collected through the two year post-op point and with questionnaires from three to seven years (FDA 510(K) Memorandum K082079 August 14, 2008).

Table 15. Patients with clinically significant improvement in pain - Acute Group

Treatment	12 months			24 months		
	#s	T	%	#s	T	%
collagen meniscus implant	49	64	77%	50	56	89%
control	52	59	88%	48	52	92%

#s = number of patient successes (clinically significant improvement in VAS mean pain score)
T= total number of patients in protocol-treatment group with a success or failure score at the post operative time-point
Clinically significant improvement (relative to pre-op) is defined as follows:

- VAS pain (mean of pain scores at highest activity, routine activity, and rest),
- post-op mean must be at least 20% lower than pre-op mean.

Table 16. Patients with clinically significant improvement in Lysholm Scores - Acute Group

Treatment	12 months			24 months		
	#s	T	%	#s	T	%
collagen meniscus implant	50	65	77%	48	57	84%
control	48	60	80%	46	53	87%

#s = number of patient successes (clinically significant improvement in Lysholm score)
T= total number of patients in protocol-treatment group with a success or failure score at the post operative time-point
Clinically significant improvement (relative to pre-op) is defined as follows for Lysholm scores:

- If pre-op is less than 80, then post-op score at time-point must be at least 20% higher.
- If pre-op score is greater than or equal to 80, then post-op at time-point must be 95 or higher.

Table 17. Patients with clinically significant improvement in self-assessment scores - Acute Group

Treatment	12 months			24 months		
	#s	T	%	#s	T	%
collagen meniscus implant	60	65	92%	54	57	95%
control	56	60	93%	52	53	98%

#s = number of patient successes (clinically significant improvement in patient self-assessment)
T= total number of patients in protocol-treatment group with a success or failure score at the post operative time-point
Clinically significant improvement in self-assessment (relative to pre-op) is defined as follows:

- If pre-op is 1(normal), then post-op score at time-point must be at least 1.

- If pre-op is 2(nearly normal), then post-op score at time-point must be at 2 or 1.
- If pre-op is 3(abnormal), then post-op score at time-point must be at 2 or 1.
- If pre-op is 4(severely abnormal), then post-op score at time-point must be 3, 2 or 1.

Table 18. Tegner Activity Level. Mean scores for acute group

	N	Pre-injury*	N	Pre-operative	N	12 month	N	24 month
collagen meniscus implant	76	6.8	76	3.1	65	4.6	57	4.9
control	80	6.3	80	2.7	58	4.6	53	4.7

*based on patient recall

The Tegner activity level was one of thirteen secondary endpoints. As per protocol, a patient would be considered a success at 24 months in the Tegner activity score was at least one grade level higher than the pre-op activity level (unless this would require them to exceed their pre-injury level).

Table 19. Patients with clinically significant improvement in pain for chronic group

Treatment	12 months			24 months		
	#s	T	%	#s	T	%
collagen meniscus implant	48	59	81%	37	45	82%
control	40	45	89%	28	36	78%

#s = number of patient successes (clinically significant improvement in VAS mean pain score)
T= total number of patients in protocol-treatment group with a success or failure score at the post operative time-point
Clinically significant improvement (relative to pre-op) was defined as follows:

- VAS pain (mean of pain scores at highest activity, routine activity, and rest),
- Post-op mean must be at least 20% lower than pre-op mean.

Table 20. Patients with clinically significant improvement in Lysholm Scores - Chronic Group

Treatment	12 months			24 months		
	#s	T	%	#s	T	%
collagen meniscus implant	45	59	76%	29	45	64%
control	35	45	78%	25	36	69%

#s = number of patient successes (clinically significant improvement in Lysholm score)
T= total number of patients in protocol-treatment group with a success or failure score at the post operative time-point
Clinically significant improvement (relative to pre-op) for Lysholm score was defined as follows:

- If pre-op is less than 80, then post-op score at time-point must be at least 20% higher.
- If pre-op score is greater than or equal to 80, then post-op at time-point must be 95 or higher.

Table 21. Patients with clinically significant improvement in self-assessment scores for chronic group

Treatment	12 months			24 months		
	#s	T	%	#s	T	%
collagen meniscus implant	55	59	93%	40	45	89%
control	39	45	87%	32	36	89%

#s = number of patient successes (clinically significant improvement in patient self-assessment)
T= total number of patients in protocol-treatment group with a success or failure score at the post operative time-point

Clinically significant improvement in self-assessment (relative to pre-op) is defined as follows:

- If pre-op is 1(normal), then post-op score at time-point must be at least 1.
- If pre-op is 2(nearly normal), then post-op score at time-point must be at 2 or 1.
- If pre-op is 3(abnormal), then post-op score at time-point must be at 2 or 1.
- If pre-op is 4(severely abnormal), then post-op score at time-point must be 3, 2 or 1.

Table 22. Tegner Activity Level - Mean scores for chronic group

	N	Pre-injury*	N	Pre-operative	N	12 month	N	24 month
collagen meniscus implant	83	6.5	82	2.9	60	4.1	45	5.0
control	68	6.6	67	3.0	44	4.1	36	4.4

*based on patient recall

The Tegner activity level was one of thirteen secondary endpoints. As per protocol, a patient would be considered a success at 24 months if the Tegner activity score was at least one grade level higher than the pre-op activity level (unless this would require them to exceed their pre-injury level).

Baseline Operative Information

More native meniscus was removed in the collagen meniscus implant group, on average, as compared to the control group. It was noted, "Hence, in more than 40% of the cases, 80% or more of the meniscus was removed from patients in the CS group." (FDA Executive Summary November 14, 2008 meeting)

Re-look arthroscopy results

"Assuming that there is no regrowth of tissue after a partial meniscectomy procedure, the data has demonstrated that the ReGen CS device does act as a scaffold to allow for tissue ingrowth with minimal inflammatory response. Also, the majority of CS devices were firmly attached to the host rim. Of note was the fact that 16% of evaluated CS devices were not firmly attached to the host rim and 18% of knee compartments were determined to be worse than during the operative procedure at the time of the re-look arthroscopic procedure." (FDA Executive Summary November 14, 2008 meeting)

Radiographic Evaluation - Change from pre-op for combined results from acute and chronic study arms (FDA Executive Summary November 14, 2008 meeting).

Table 23. Radiographic evaluation combined for acute and chronic arms

Parameter evaluated	**12 months**			**24 months**		
	collagen meniscus implant	**control**	**p-value**	**collagen meniscus implant**	**control**	**p-value**
Osteophyte formation worsens ≥ 1 grade	15/64 (23%)	16/66 (24%)	1.00	19/72 (26%)	26/78 (33%)	0.38
Fairbank – Ridge Formation worsens ≥ 1 grade	5/64 (8%)	1/64 (2%)	0.21	10/71 (14%)	7/73 (10%)	0.45
Fairbank – flattening of femoral condyle worsens ≥ 1 grade	16/64 (25%)	20/64 (31%)	0.56	25/71 (35%)	25/73 (34%)	1.00
Fairbank –Joint space narrowing worsens ≥ 1 grade	21/64 (33%)	20/64 (31%)	1.00	30/71 (42%)	23/73 (32%)	0.23

Parameter evaluated	12 months			24 months		

It was noted in the Executive Summary, "The percentage of patients (Combining Acute and Chronic groups) experiencing a change of one or more grades in osteophyte formation or Fairbank changes was not statistically significant between CS and control at 12 or 24 months." (FDA Executive Summary November 14, 2008 meeting)

4. Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) Meeting.

CMS did not hold a MEDCAC meeting on this topic.

5. Evidence-based guidelines

No evidence-based guidelines were identified.

6. Public Comments

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

Initial Public Comments

CMS received thirty-one comments during the initial public comment period. Of the thirty-one comments, twenty-six comments were submitted by physicians. Of the physician commenters, one was a patient that had a collagen meniscus implant and one was the inventor of the collagen meniscus implant. One comment was submitted by the manufacturer of Menaflex™. One comment was submitted by a healthcare system from one of their provider sites, one comment was submitted by a health insurance company, and one comment was submitted by a health research group. There were twenty-eight comments that either supported coverage for the collagen meniscus implant or felt that Medicare should not develop a national coverage determination. Three comments supported non-coverage for the collagen meniscus implant. The complete text of these comments is available on the CMS website at http://www.cms.gov/mcd/viewpubliccomments.asp?nca_id=235 .

Public Comment on the Proposed Decision Memorandum

CMS received only one comment on the proposed decision memorandum. The commenter felt that it was unfair to deny medical services to someone because they are on Medicare and expressed concern about age discrimination.

Response: National coverage determinations establish national coverage policy for the Medicare program. Our decisions are based on whether the evidence is sufficient to conclude whether an item or service, in this case the collagen meniscus implant, will improve health outcomes for Medicare beneficiaries. This decision is not based on age and it applies to all Medicare beneficiaries. After a thorough review of the evidence, we concluded that the evidence shows that the collagen meniscus implant does not improve health outcomes.

VIII. Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act §1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions the items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A) of the Act.

The question of interest for this evidentiary review and analysis is:

Is the evidence sufficient to conclude that meniscus repair with collagen meniscus implant will improve health outcomes in the Medicare population with meniscal damage?

This section presents the agency’s evaluation of the evidence considered and conclusions reached for the assessment.

The menisci provide mechanical support, localized pressure distribution, and lubrication to the knee joint. Therapies have changed over the years to excising less tissue in an effort to possibly decrease the risk of later degeneration, attempting to keep symptoms of knee pain at bay and preserve knee function. Meniscal tears are generally grouped into traumatic and degenerative tears, however, there is no way to differentiate between the two in the older population by exam or symptoms (Menetrey et al. 2002). Little high quality evidence for the treatment of meniscal tears exists in the published literature. There is no published guideline for treatment of meniscal tears or universally accepted or clear definitions.

Meniscal tears are common in a variety of age groups, and treatments aimed at improving patient outcomes continue to emerge, despite the fact that, "we still lack knowledge as to the loads to which the normal knee is subjected," to better guide treatment (Messner and Gao 1998). "In the early 1990s, Stone, Steadman and Rodkey developed the CMI" (Buma et al.). The collagen meniscus implant was developed as a temporary scaffold for tissue ingrowth, with the desired outcome that the meniscus defect would be filled with functional tissue and this would perform essentially the same function as the meniscus, i.e., a regenerated meniscus. The device was placed after partial meniscectomy as an additional procedure. It was not a complete meniscus replacement, as it required both horns (rims) to be intact so it could be sutured in place. However, in Rodkey et al. (2008) (and the FDA data), more meniscal tissue was removed from the treatment patients than in the control patients – the partial meniscectomy patients. The implant remains in place until it is resorbed. Even though the implant is resorbable, ReGen CS resorbed in only 40% of cases at one year (as judged by 55/136 biopsies had no CS remnants), it would stand to reason there must be some type of functional requirements (mechanical, stability, lubrication) in the interim before resorption occurs. In the FDA 510(K) Memorandum K082079 August 14, 2008, it was stated: "The sponsor did not provide a comparison of the tensile strength or suture pull -out strength of human meniscus compared to the tensile strength or suture pull-out strength of the CS device. …However, based upon data provided in the canine study, it appears that the suture pull-out strength of the CS device is significantly less than the suture pull-out strength for native meniscal tissue (i.e., 4.2-7.5 lb for the CS device as compared to 25.7lb for the native canine meniscal tissue). …Therefore, it appears that the ReGen CS device does not meet the first criterion identified by our Panel member, Dr. Skinner (in his review of K063827), where he stated that to demonstrate efficacy that, '*first, the ReGen CS must show that it has mechanical properties that approximate the removed meniscus*.' "

The data from the randomized controlled trial, also reported in a medical journal by Rodkey et al. (2008), was submitted to the FDA for device evaluation. The data reported in the journal article were different from the data submitted to the FDA. Since the FDA analysis involved the complete raw data from the clinical trial, it was more complete than what was presented in Rodkey et al. (2008). Publications of trials should convey information to the reader about how it was conducted and analyzed in a transparent manner. When studies are not reported in their totality using standard methodology such as CONSORT (Consolidated Standards of Reporting Trials), they are subject to bias and can lead to misinterpretation or confusion. The check list of items for CONSORT is referenced in the published literature.

The Rodkey article reported patient benefit of the collagen meniscus implant based on one measure – the Tegner Index. The Tegner Index was not a pre-specified primary or secondary effectiveness endpoint. The measure that was related to it, the Tegner activity level, was one of thirteen secondary endpoints and had a predefined success criteria. The article did not provide the statistical analysis for the a priori dichotomized Tegner activity level according to the study protocol (FDA Brief Statistical Review of 510(K) K082079 Aug 11, 2008). Further, the FDA noted that in the application the sponsor stated that the clinical significance of the Tegner index had not been reported in the literature. It was not clear how useful the Tegner index was as a measure. The FDA noted, "It does not appear to take into account that individuals may be able to participate at a higher level of activity but consciously choose not to or that some people will participate at a higher level of activity but with limitations." (FDA Executive Summary November 14, 2008 meeting).

The Rodkey et al. (2008) article did not identify the pre-specified primary effectiveness endpoints. This can mislead readers into thinking that that the study design was to show the device's superiority over the control group in the Tegner Index as opposed to the actual a priori primary endpoints (FDA 510(K) Memorandum K082079 August 14, 2008). The clinical data failed to detect a significant difference in the primary measures (identified in FDA documents): VAS score, Lysholm score and patient self-assessment score. Only the Tegner index - a post-hoc created, unvalidated measure with no reported clinical significance - was found to be the reported patient benefit in only the chronic arm of the study group. We do not find this evidence to be compelling to demonstrate that the collagen meniscus implant improves health outcomes.

The FDA data review questioned the safety of the collagen meniscus implant device (FDA 510(K) Memorandum K082079 August 14, 2008). The number of reoperations in the chronic arm as reported in Rodkey et al. (2008) (Table 10) was less than what was identified by the FDA data analysis (Table 14). Five re-operations in the control patients and seventeen reoperations in the device patients were not included in the Rodkey et al. (2008) reoperations table for various reasons. It was noted that the manner of reporting by the FDA reviewers was consistent with FDA's usual procedure in determining safety outcomes. As noted in the FDA Executive Summary, "The procedures performed during the re-look appear to confound the interpretation of the re-operation data between the two groups." From a patient's perspective: a reoperation is a reoperation, and there are more reoperations related to the device in this study. Also noted in the FDA information, there appeared to be eight explants (all reported patients, acute and chronic) (FDA 510(K) Memorandum K082079 August 14, 2008). These eight explants were not explicitly accounted for in the article by Rodkey et al. (2008).

Other safety data differed as well. It was difficult to match data from Rodkey et al. (2008) -Table 9 "Serious or Clinically relevant complications in the Study Knee" to the FDA data - Table 12 "serious" and "serious device related" adverse events. The surgeon-investigator at each site determined the seriousness of each complication and whether it was related to the implant. This may lead to incomplete reporting of events as in Rodkey et al. (2008) and seemed to have done so in this case. From the FDA data of the clinical trial, the collagen meniscus implant patients experienced a higher serious adverse event rate than the control group and from what was reported in the Rodkey et al. (2008) article (FDA 510(K) Memorandum K082079 August 14) raising a safety concern.

Meniscectomy fell out of favor in the medical community due to studies demonstrating degenerative changes. The collagen meniscus implant has not been demonstrated in the published medical literature to change the progression of degenerative joint disease compared to partial meniscectomy.

Even though there were reports of a European trial/experience, the published clinical efficacy data involved only case series reports of 46 patients (Zafferini, Bulgheroni, Reguzzoni). Case series data cannot be used to draw inferences for treatment effect due to the lack of a comparator group. Without a comparator group it is not possible to identify what is causing the treatment effect due to the other variables that are present. Additionally, the FDA stated, "The OUS Marketing Experience results appear questionable as there were only 3 reported complaints of 1898 devices sold. This is not in line with the results in the IDE trial and questions the way in which this data is reported" (FDA 510(K) Memorandum K082079 August 14).

Providing a scaffold for tissue regrowth is theoretically promising. For the collagen meniscus implant, at the one-year re-look new tissue was present. However, the FDA noted, "based on the pictures of the biopsy samples taken during the one year re-look arthroscopy for CS patients showed that there was no transformation of the CS material in to a fibrous cartilage, e.g., meniscus, in any degree" (FDA 510(K) Memorandum K082079 August 14, 2008). There was no evidence that tissue re-growth in the area of the device implant was associated with any clinical benefit (FDA Clinical Review K063827s1 August 3, 2007).

None of the trials included patients over the age of sixty. When trials do not include patients in the older Medicare population, we must consider if the evidence is generalizable to this older population. There is no evidence of benefit of improved outcomes in the study population for the collagen meniscus implant and this outcome of no benefit is generalizable to the older Medicare population.

Summary

There were six small observational clinical case studies and one randomized controlled trial (RCT) for the collagen meniscus implant identified and reviewed. The RCT was designed to show superiority of the collagen meniscus implant with partial medial meniscectomy compared to partial medial meniscectomy alone. The RCT failed to show superiority on any of the a priori primary endpoints – pain, function, patient satisfaction. Although the Tegner index was reported to show a patient benefit in the treatment group of the chronic arm of the RCT, this was not a pre-specified primary or secondary endpoint for the trial. In fact, the Tegner index was an author-defined measure based on the Tegner activity score and has not been validated as an outcome measure nor has its clinical significance been reported in the literature. The Tegner index fails to meet any evidentiary standard to show a benefit of improved patient outcomes for this device.

The FDA analysis of the adverse events data is concerning and brings into question possible patient harms related to the collagen meniscus implant. In addition, the discrepancy in the adverse events reported in the published article on the RCT and the data provided to the FDA is disconcerting. Discrepancies in reported patient outcomes data also creates concerns about the reliability of study results published in peer reviewed journals and begs the question of what resources can be relied on with confidence to make evidence based decisions in healthcare. The reported reoperation rate data is potentially biased by the additional procedures performed during the protocol-specified re-look procedures on the treatment group in the trial. The RCT for the collagen meniscus implant failed to meet any of the primary endpoints in the trial.

IX. Conclusion

The CMS has concluded that the collagen meniscus implant does not improve health outcomes in the Medicare population. Therefore, CMS has determined that the collagen meniscus implant is not reasonable and necessary for the treatment of meniscal injury/tear and we are issuing a national non-coverage determination under §1862(a)(1)(A) of the Social Security Act.

Appendix A

General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

>The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Collagen Meniscus Implant
Appendix B

Source of this appendix is the FDA Executive Summary November 14, 2008 meeting.

Table 1. Objective: Monitoring the Safety

Endpoint/Measure	Success	Failure
Blood Analysis (ELISA)	Less than or equal to 2 standard deviations from the mean immune response to the implant	Greater than 2 standard deviations from the mean immune response to the implant
Adverse Events	No significant adverse events documented as attributable to the implant	Significant adverse events documented as attributable to the implant

Table 2. Objective: Demonstrate clinical benefit to the patient

Endpoint/Measure	Success	Failure	Time point of Success/Failure Determination
Arthroscopic Appearance	Implant/new tissue complex remains firmly attached to host rim and at least 60% of original defect remains filled	implant/new tissue complex does not remain firmly attached to host rim and/or less than 60% or original defect remains filled	12 mo.
histopathology			12 mo.

Endpoint/Measure	Success	Failure	Time point of Success/Failure Determination
	Indication of cellular ingrowth into the implant and indication of new extracellular matrix deposition	Absence of cellular ingrowth into the implant and/or no new extracellular matrix deposition	
pain	VAS pain scale improved by at least 20% compared to pre-op	VAS pain scale did not improve by at least 20% compared to pre-op	24 mo.
swelling	Increase in knee circumference at the mid-patella less than or equal to 6 cm. compared to pre-op	Increase in knee circumference at the mid-patella greater than 6 cm. Compared to pre-op	24 mo.
Lysholm Knee Scoring Scale	For patients with pre-op score < 80, increase in score of at least 20% compared to the pre-op score. For patients with pre-op score $\geq$ 80, a final score of $\geq$ 95	For patients with pre-op score < 80, increase in score of less than 20% compared to the pre-op score. For patients with pre-op score $\geq$ 80, a final score of $\leq$ 95	24 mo.
Patient's own Evaluation/Overall Assessment	Improvement of at least one grade from pre-op. If pre-op grade was “normal” or “nearly normal”, then no decrement.	Lack of improvement of at least one grade from pre-op. If pre-op grade was “normal” or “nearly normal”, then decrement to lower grade.	24 mo.

Table 3. Other endpoints

Additional endpoints:	Success	Failure
Synovial fluid	No evidence of significant inflammatory response with less than or equal to 2,000 white blood cells per ml.	Evidence of significant inflammatory response with greater than 2,000 white blood cells per ml.
redness	Redness categorized as slight or none.	Redness categorized as moderate or severe.
Skin/Superficial wound healing	None to mild exudate is present in 6 weeks or less.	Moderate to severe exudate is present requiring on-going wound care for greater than 6 weeks.

Additional endpoints:	Success	Failure
Range of motion	Show improvement if their pre-op score for the injured knee was worse than the non-involved knee, or return to their preop score if the injured knee at pre-op was the same or better than the non-involved knee.	No improvement if their pre-op score for the injured knee was worse than the non-involved knee, or did not return to their pre-op score if the injured knee at pre-op was the same or better than the non-involved knee.
Thigh girth measurement	Show improvement if their pre-op score for the injured knee was worse than the non-involved knee, or return to their pre-op score if the injured knee at pre-op was the same or better than the non-involved knee	No improvement if their pre-op score for the injured knee was worse than the non-involved knee, or did not return to their pre-op score if the injured knee at pre-op was the same or better than the non-involved knee.
Functional evaluation	The patient improves by at least one grade level if the pre-op score was a 4, 5, or a 6 (Severe limitation to not allowed). If the pre-op score was a 1, 2, or 3 (Limitation is none to moderate), the score must not worsen.	The patient regresses or remains at the same grade level if the pre-op score was a 4, 5, or a 6 (Severe limitation to Not allowed). If the pre-op score was a 1, 2, or 3 (Limitation is none to moderate), the score worsens.
Tegner activity level	The patient's score is at least one grade level higher than the pre-op activity level, unless this would require them to exceed their pre-injury level.	The patient's score is the same as or worse than the re-p[activity level, unless their pre-op score was the same or higher than their pre-injury score.
Radiographic evaluation	No *significant increase in osteophytes or other degenerative joint changes compared with the same views of pre-op baseline radiographs *A significant increase is defined as at least one grade deterioration (i.e., make to moderate) in osteophyte formation and worsening in at least two of the three Fairbanks criteria (ridge formation, flattening of the femoral condyle and joint space narrowing).	Baseline radiographs
Gross appearance of regeneration	Evidence of regeneration based upon description in protocol	No evidence of regeneration based upon the above description.
Implant appearance		

Additional endpoints:	Success	Failure
	Implant appears mostly smooth, with no significant irregularities. Surface does not have a cobblestone appearance with pitting; inner rim does not have a jagged “sawtooth” appearance.	Implant does not appear mostly smooth, and there are significant irregularities. Surface has cobblestone appearance with pitting rim has jagged “sawtooth” appearance.
Implant-host stability	Implant appears stable on probing. Probing does not reveal tears or other integrity interruptions, nor demonstrate a lack of adherence to the host meniscal rim.	Implant does not appear stable on probing. Probing reveals tears or other integrity interruptions, or demonstrates a lack of adherence to the host meniscal rim.
Presence of loose bodies or fraying	No significant loose bodies or fraying which cause mechanical dysfunction of the joint (such as constant and persistent catching or locking).	Significant loose bodies or fraying which cause mechanical dysfunction of the joint (such as constant and persistent catching or locking).
Implant-host junction	Grades will be assigned based on the degree of “healing” between the implant and host tissue and recorded: 0=Clear separation between host tissue and implant. No interdigitation; gaps in tissue not an artifact of sampling; 1= Slight integration; 2= Moderate integration; 3= Fully healed; and 4= Interface not observed (N/A) • SUCCESS: A grade of “2” or “3” • FAILURE: A grade of “0” or”1”	
Presence of inflammatory response	Evidence of an inflammatory response that is graded as none or mild.	Evidence of a significant inflammatory response that is graded as moderate or severe.

150.12. – Collagen Meniscus Implant (Effective May 25, 2010)

150.12 – Collagen Meniscus Implant (Effective May 25, 2010)
(Rev.)

A. General

The knee menisci are wedge-shaped, semi-lunar discs of fibrous tissue located in the knee joint between the ends of the femur and the tibia and fibula. There is a lateral and medial meniscus in each knee. It is known now that the menisci provide mechanical support, localized pressure distribution, and lubrication of the knee joint. Initially, meniscal tears were treated with total meniscectomy; however, as knowledge of the function of the menisci and the potential long term effects of total meniscectomy on the knee joint evolved, treatment of symptomatic meniscal tears gravitated to repair of the tear, when possible, or partial meniscectomy.

The collagen meniscus implant (also referred to as collagen scaffold (CS), CMI or MenaflexTM meniscus implant throughout the published literature) is used to fill meniscal defects that result from partial meniscectomy. The collagen meniscus implant is not intended to replace the entire meniscus at it requires a meniscal rim for attachment. The literature describes the placement of the collagen meniscus implant through an arthroscopic procedure with an additional incision for capture of the repair needles and tying of the sutures. After debridement of the damaged meniscus, the implant is trimmed to the size of meniscal defect and sutured into place. The collagen meniscus implant is described as a tissue engineered scaffold to support the generation of new meniscus-like tissue. The collagen meniscus implant is manufactured from bovine collagen and should not be confused with the meniscus transplant which involves the replacement of the meniscus with a transplant meniscus from a cadaver donor. The meniscus transplant is not addressed under this national coverage determination.

B. Nationally Covered Indications

N/A

C. Nationally Non-Covered Indications

Effective for services performed on or after May 25, 2010, CMS has determined that the evidence is adequate to conclude that the collagen meniscus implant does not improve health outcomes and, therefore, is not reasonable and necessary for the treatment of meniscal injury/tear under section 1862(a)(1)(A) of the Social Security Act. Thus, the collagen meniscus implant is non-covered by Medicare.

D. Other

N/A

(This NCD last reviewed May 2010.)

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